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TITLE: Improving the Efficiency and Efficacy of Glibenclamide in Limiting Progressive Hemorrhagic Necrosis Following Traumatic Spinal Cord Injury

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14. ABSTRACT Preclinical work has demonstrated that glibenclamide administration improves outcomes in rat models of spinal cord injury, with the principal mechanism of action being amelioration of post-traumatic hemorrhagic necrosis (PHN). We hypothesize that some but not all patients with spinal cord injury, principally those with incomplete lesions, will respond to glibenclamide therapy. Our goal is identify early markers of injury that can be used to predict which patients may benefit from glibenclamide treatment. In this proposal, we will measure early biological markers of injury severity, specifically, serum biomarkers and T2 MRI findings obtained within hours of injury. We will subsequently correlate these early abnormalities with 6-month neurological examinations. During the first year of this grant, the notice of award was received on February 23, 2011, and the first patient was enrolled 5/29/11. As of the time of this report, we have screened 18 patients of which 6 patients have been enrolled. Another important development is that we recently broadened entry criteria to include additional patients with incomplete lesions, specifically those with central cord syndrome. This minor change is expected to significantly increase enrollment of patients with incomplete lesions.					
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INTRODUCTION:

The magnitude of acute post-traumatic hemorrhagic necrosis (PHN) is an early prognostic indicator of long-term functional recovery in human spinal cord injury (SCI). Recent preclinical data indicate that PHN can be reduced and functional recovery improved in spinal injured rats using glibenclamide, an FDA approved anti-diabetic drug that targets SUR1 receptors on endothelium and neurons. The range of injuries experienced by humans with SCI includes two major subclasses: (i) those that are neurologically complete within 24 hours post-injury and that are largely untreatable by available methods; (ii) those that are incomplete but are at risk to slowly evolve into complete lesions as a result of PHN. We hypothesize that only a subset of spinal cord injuries, principally those that are incomplete, will respond to glibenclamide therapy. In this proposal (the clinical portion of the overall proposal), we will examine this hypothesis. Specifically, T2 MRI will be used to measure acute hemorrhage and edema at sites of SCI across a range of human SCI patients with diverse neurological (ASIA) scores. Serum biomarkers will be analyzed. A correlation of ASIA scores at 6 months and MRI and biomarker panels obtained at 6-8 hrs will be used to assess how initial hemorrhage and select biomarkers predict long-term neurological recovery.

BODY:

This section of the report shall describe the research accomplishments associated with each task outlined in the approved Statement of Work. Data presentation shall be comprehensive in providing a complete record of the research findings for the period of the report. Provide data explaining the relationship of the most recent findings with that of previously reported findings. Appended publications and/or presentations may be substituted for detailed descriptions of methodology but must be referenced in the body of the report. If applicable, for each task outlined in the Statement of Work, reference appended publications and/or presentations for details of result findings and tables and/or figures. The report shall include negative as well as positive findings. Include problems in accomplishing any of the tasks. Statistical tests of significance shall be applied to all data whenever possible. Figures and graphs referenced in the text may be embedded in the text or appended. Figures and graphs can also be referenced in the text and appended to a publication. Recommended changes or future work to better address the research topic may also be included, although changes to the original Statement of Work must be approved by the Army Contracting Officer Representative. This approval must be obtained prior to initiating any change to the original Statement of Work.

Considerable delay in start-up of the project was occasioned by the protracted period of time that was required to gain IRB approval for this project. Fortunately, we were greatly aided in this endeavor by the grants specialist, Ms. Lori Walther. Notice of the award was received on February 23, 2011.

Subsequent to our receipt of the notice of award, the local infrastructure was put into place, including the holding of meetings with relevant health care professionals in the Emergency Department of Shock Trauma Center, and establishment of a collaborative agreement between Neurosurgery and Orthopedic Surgery at Shock Trauma Center that would allow us in Neurosurgery to recruit patients with spinal cord injury assigned to Orthopedic Surgery.

To date, we have screened 18 patients. Of the 18, 12 were not enrolled – 2 refused; all the rest had applicable exclusion criteria, including age, >8 hours since injury (transfers from other hospitals), Spanish-only speaking, gunshot wound; in addition, several patients had central cord syndrome, which to date has been an exclusion criterion (but see below). Thus, to date, we have enrolled 6 patients. The 1st patient was enrolled 5/29/11 and the 6th patient was enrolled 9/18/11. Obviously, given the time frame involved, the 6-month data have not been obtained on these patients.

Recently, we recognized the need to boost patient recruitment, especially of patients with incomplete spinal cord injuries. To this end, we sought and gained IRB approval for the minor modification to include patients with central cord syndrome. This addition will be very important not only to obtain greater numbers for enrollment, but also for increase the dynamic range of injury severity that we will be able to study.

To date, no analysis of the data has been carried out.

KEY RESEARCH ACCOMPLISHMENTS:

Bulleted list of key research accomplishments emanating from this research.

- frank start of patient enrollment for the biomarker study
- broadening of the scope of inclusion criteria to include more patients with incomplete injuries, specifically, central cord syndrome

REPORTABLE OUTCOMES:

Provide a list of reportable outcomes that have resulted from this research to include: manuscripts, abstracts, presentations; patents and licenses applied for and/or issued; degrees obtained that are supported by this award; development of cell lines, tissue or serum repositories; informatics such as databases and animal models, etc.; funding applied for based on work supported by this award; employment or research opportunities applied for and/or received based on experience/training supported by this award

- none to date

CONCLUSION:

Summarize the results to include the importance and/or implications of the completed research and when necessary, recommend changes on future work to better address the problem. A "so what section" which evaluates the knowledge as a scientific or medical product shall also be included in the conclusion of the report.

- patient recruitment is proceeding well, and due to the minor modification noted, is expected to increase.

REFERENCES:

List all references pertinent to the report using a standard journal format (i.e. format used in *Science*, *Military Medicine*, etc.).

None

APPENDICES:

Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

None

SUPPORTING DATA:

All figures and/or tables shall include legends and be clearly marked with figure/table numbers.

None